Remarks

Claims 18 and 26 are pending. Claim 25 is canceled. Support for the amendment to claim 18 can be found in canceled claim 25.

In the Office Action dated March 10, 2005, the Examiner states that claims 18 and 25-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner objects to the phrase "wherein the subject is not a rat." The applicant respectfully traverses this rejection. However, in an effort to forward prosecution, applicant has removed this phrase from the claim. Therefore, Applicant respectfully requests withdrawal of this rejection.

The Examiner has rejected claims 18 and 25-26 under 35 U.S.C. 103(a) as being unpatentable over Luo et al. in view of Zhang et al. The applicant respectfully traverses this rejection, and offers the following arguments in response.

The Luo publication demonstrates that galanin inhibits spinal cord electrical hyper-excitability for 60 minutes following nerve section (see Figure 3), at which point the animals were sacrificed. Galanin was administered 30 minutes before the nerve injury as a single bolus injection of 2.4nM (low dose) directly into the space surrounding the bottom part of the spinal cord (intrathecal (IT) administration into the lumbar enlargement, see page 163, paragraph headed "Effect of galanin" and Figure 3 of Luo et al.). That is, the galanin is delivered into the cerebrospinal fluid (CSF). The Luo publication deals exclusively with neuropathic pain and spinal cord excitability, not with peripheral nerve regeneration as claimed in the patent

application. In fact, there is no evidence of any nerve regeneration in the method and publication of Luo et al.

When damage or injury to sensory or motor nerves (in Luo et al. in the sciatic nerve) occurs, this triggers a cascade of molecular events within the cell body of that nerve, the dorsal root ganglion (DRG), which in turn attempts to repair the damage and restore the normal function of the nerve, so-called nerve regeneration. The Protein Kinase C (PKC) and MAP Kinase (MAPK) intra-cellular signalling cascades have both been shown to up-regulate after nerve injury and are essential for nerve regeneration (Klinz & Heumann (1995) J. Neurochem. 65 1046-53; Kiryu et al. (1995) Brain Res. Mol. Brain Res. 29 147-56; Kitahara et al. (1994) Neurosci. Res. 20 275-280; attached). At the 1996 priority date of the current patent application, no published literature existed to indicate that galanin speeded up nerve regeneration, nor that it activated PKC or MAPK.

It is the Examiner's contention that, in the 90 minutes following the intrathecal administration of galanin into the lumbar enlargement and before the animal was sacrificed, that "...the preliminary beginnings of regeneration..." could have begun and that this is encompassed by claim 18 (page 4 of Office Action, last sentence). The scientific facts do not support this contention. For regeneration to have occurred in the animals used in the experiments of Luo et al. during the 90 minute period before the animals were sacrificed, the galanin would have had to gain access to the cell bodies in the DRG, since this is where the intra-cellular pro-regenerative machinery resides (Liuzzi & Tedeschi (1991) Neurosurgery Clinics of N. America 2 31-42; Pollock (1995) Curr. Op. Neurology 8 354-358; Terenghi (1994) J. Anatomy (Pt I) 1-14;

attached). The only way that galanin, when applied to the space surrounding the bottom part of the spinal cord, could have reached the cell bodies of the sensory neurons in the DRG which is where "...the preliminary beginnings of regeneration..." would have occurred, is by direct uptake of the galanin by the nerve terminals in the dorsal horn of the spinal cord. It should be noted that the cell bodies of the sensory neurons of the DRG lie outside the central nervous system (CNS), whilst the spinal cord is part of the CNS. The cerebrospinal fluid (CSF) that bathes the spinal cord is not in contact with the DRG and thus galanin could not have reached the DRG by passive diffusion.

There are well documented and active transport mechanisms in sensory neurons that move proteins from the nerve terminals of the spinal cord or the ends of the peripheral axons of the sciatic nerve to the cell body in the DRG, termed retrograde transport. A number of these retrograde transport mechanisms for Nerve Growth Factor (NGF) and Horseradish Peroxidase (HRP) have been extensively studied and characterized. There is good agreement between these published papers that the rate at which these retrograde transport processes move proteins from the rat dorsal horn of the spinal cord to the cell body in the DRG is a maximum rate of 7.5 mm/hour (range 2.5 – 7.5 mm/hr, Yip and Johnson, Jr. (1986) J. Neurocytol. 15 789-98; Richardson and Riopelle. (1984) J. Neurosci. 4 1683-9; attached).

The applicant has measured the length of the nerve root (i.e. the part of the nerve that connects the cell bodies of the DRG to the dorsal horn of the spinal cord) from a total of 21 nerve roots which were harvested from the lumbar region of 5 female Sprague-Dawley rats weighing 200-250g (as used in the experiments of Luo et al.). The length of the nerve root was then

measured using a calibrated graticule and a dissecting microscope and the mean length was found to be 18.5±0.9 mm (see Declaration from Dr. Wynick, attached). This figure is in good agreement with the findings of Michael et al. (Michael et al. (1997) J. Neurosci. 17 8476-8490, attached) who found the nerve root of adult male Wistar rats (200-400g body weight) to be 17 mm. Similarly, Baba et al. (Baba et al. (1999) J. Neurosci. 2 859-867, attached) found the dorsal root to be between 18-20 mm in adult male Sprague-Dawley rats weighing 300-350g.

Based on the above findings, assuming the maximum rate of retrograde transport of galanin from the dorsal horn of the spinal cord to the DRG is 7.5 mm/hr and the length of the nerve root between the dorsal horn of the spinal cord and the DRG is at least 17mm in length (Declaration, attached), then the galanin would only have been transported 11.25 mm in the 90 minutes after galanin was administered before the animals were sacrificed (i.e. about two thirds of the way to the DRG). Galanin could not, therefore, have even begun to affect regeneration in the DRG cell bodies by the time the experiment was terminated.

It should also be noted that the concentration of galanin would have immediately and rapidly begun to fall after the administration of the bolus injection of 2.4nM galanin. This would have occurred within seconds, as the galanin would have been diluted by the CSF and almost immediately would also have started to be degraded by proteolytic enzymes in the CSF (Bedecs et al. (1995) Neuropeptides 29 137-43, attached). Therefore, even in the highly unlikely event that a small proportion of the galanin that was administered by bolus-dose to the spinal cord did reach the DRG by retrograde transport, the final dose would be at least 100-fold lower than that originally administered IT (in the sub-nanomolar range, page 163 and Figure 3 of Luo et al.). In

contrast, the dose of galanin demonstrated to stimulate nerve outgrowth from sensory neurons by direct application in cell culture to the DRG cell body is at least 100nM galanin (Mahoney et al. (2003) J. Neurosci. 23 416-421, attached). In light of this, the concentration of galanin that would have reached the DRG would have been at least 2000-fold lower than that necessary to stimulate regeneration, again making it nearly impossible that galanin could have even begun to affect regeneration in the DRG cell bodies by the time the experiment was terminated.

Finally, even if galanin were transported to the DRG in the 90 minute time period, it would have been on the inside of the DRG cell body. The galanin receptors are on the outside of the same neuronal cell body and so the only way the galanin could affect regeneration is if it were further transported to the distal cut end of the nerve and then activated galanin receptors there. The pro-regenerative signal from the activation of these galanin receptors would have then needed to be transported back to the DRG before it could affect regeneration. Since the distance from the DRG to the cut end of the sciatic nerve is at least 2cm, the time taken for that process would have been very many hours and could not occur within the 90 minutes between application of the galanin to the spinal cord and the sacrifice of the animals, as carried out in the experiments of Luo et al.

For these reasons, one of ordinary skill in the art would have no incentive, on reading the Luo publication, to imagine that nerve regeneration in the severed sciatic nerve would have begun during the time period utilized in the experiments of Luo et al. In addition, in light of the Luo et al. disclosure and on reading the disclosure in Zhang et al. that galanin may be suitable for use as an analgesic in humans, one of ordinary skill in the art would have no motivation to

administer a galanin agonist in a method for the treatment of peripheral nerve damage, wherein the peripheral nerve damage is treated by nerve regeneration, as claimed in claim 18 as amended.

The applicant therefore request removal of this basis for rejection and allowance of claims 18 and 26 to issue.

Pursuant to the above amendments and remarks, consideration and allowance of the pending application is believed warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

No fee is believe due. However, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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Janell J. Cleveland — June 10, 2005

Janell T. Cleveland — Date